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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

MIMI ADACHI, KEICHI NAKAYAMA, SHIGETAKA KITAJIMA, and

HIROMITSU TAKAGI

Appeal 2010-007915
Application 10/580,248
Madison Building - East Wing

Oral Hearing Held: Tuesday, September 13, 2011

Before TONI R. SCHEINER, DONALD E. ADAMS, and

JEFFREY N. FREDMAN, Administrative Patent Judges

ON BEHALF OF THE APPELLANT:

ALEXANDER H. SPIEGLER, ESQ.

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The above-entitled matter came on for hearing on Tuesday, September 13, 2011, commencing at 9:09 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, 9th Floor, Alexandria, Virginia, before Kevin Carr, Notary Public.

THE CLERK: Good morning. Calendar No.15, Appeal No. 2010-007915. Mr. Spiegler.

JUDGE SCHEINER: Good morning.

MR. SPIEGLER: Good morning.

JUDGE SCHEINER: Before we get started, if you have a card for the court reporter that would be great. And if you'd like to, also introduce your colleagues for the record.

MR. SPIEGLER: Yes.

JUDGE SCHEINER: -- saying other user -- good morning. You can get started whenever you're ready. You will have twenty minutes.

MR. SPIEGLER: Okay, great. May it please the court, my name is Alex Spiegler and I represent the appellants. This is relatively a straightforward case. The claims relate to methods for proliferating cardiomyocytes by introducing three elements into the cardiomyocytes; a cyclin, a cyclin-dependent kinase, and a gene encoding effector that inhibits the production or function of a KIP protein.

There's no dispute in this case that the primary reference teaches the first two elements. The only dispute here is whether it's obvious to combine the secondary four references to obtain element C, and then to

combine that hypothetical teaching with the primary reference, which teaches A and B.

We maintain that it would not have been obvious to do this for four reasons. The combination of references does not teach element C. Even assuming it did teach element C, there's no reason to combine that hypothetical teaching with the primary reference. There's no reasonable expectation of success, and the specification discloses unexpected results.

In this hearing we plan to really focus on the last three reasons. Our rationale in this case is actually based on evidence disclosed in the specification. This is evidence that the Examiner has either ignored or misinterpreted, in our position. As such we request that you reverse the Examiner's rejection, based on the arguments that we're going to present.

So, as I mentioned -- let's just start from the viewpoint of -- we assume that the four references teach element C. We're just going to assume that for argument's sake. We don't agree with that, but we're going to assume that. The specification actually teaches an example -- actually, two examples, examples four and five, that demonstrate that if one of skill in the art had element C they would find that if they took element C, introduced it into a cardiomyocyte that they would have no increase in proliferation.

So in view of that evidence we believe that one of skill in the art would not combine that understanding with A and B. Essentially, if you have evidence that says you get no increase in proliferation, why would you combine that with something else?

The Examiner in this case -- we've made this argument on several occasions and the Examiner has not really addressed this. And

actually, at the end of the Examiner's answer on page 20 the Examiner basically asserts that what we're arguing is not in the claims and, you know, what we're really showing here is the evidence against why someone would have tried to combine these references.

So this is actually kind of a unique case in the sense that we're not simply arguing just in the abstract there's no reason to combine. We actually have the evidence to show you why one of skill in the art wouldn't have combined it at the time of the invention. And we think that that actual evidence is more persuasive than simply arguments that the Examiner is making.

We've cited in our Reply Brief the case of Proctor & Gamble v. Teva, and we simply cited that case to help demonstrate that the federal circuit has shown that when you have evidence showing that things are not reasonably likely to happen that you wouldn't have -- there's no reason to combine references to -- there's no reason to combine the references and there's no reasonable expectation of success. Our description of that case is on pages six and seven of the Reply Brief.

JUDGE FREDMAN: The question is -- you're kind of relying essentially on Figure 8 to say, I think, that the inclusion of the SKP2, which is, I think, your element C --

MR. SPIEGLER: Correct.

JUDGE FREDMAN: -- doesn't really have any effect. But you kind of see that it has sort of a twofold effect and when you talk about the control, the control here is a vector that presumably -- anything. You -- what you don't really have is a sort of true control, which is without the

inclusion of the vector. You know, frequently, when you put a vector into a cell, the vector alone will have some effect --

MR. SPIEGLER: Mm-hmm.

JUDGE FREDMAN: -- on the cell. The fact that you have all the other factors in the vector, just the sort of control regions, and when you look at the various values you have, you have a twofold effect from SKP2. And you have the next one, which is the D1NLS plus cdk4 -- you have clearly over a threefold effect. When you have all three you have a fivefold effect. Well, two and three do add up to five I think.

MR. SPIEGLER: Yeah. So I --

JUDGE FREDMAN: So it seems additive.

MR. SPIEGLER: So we are relying on Figure 8 and Figure 10. And Figure 10 also helps prove the point as well. In that case the control and the p27 siRNA are essentially giving you the same results, which is --

JUDGE ADAMS: Wait. We're talking about two different things here. Let's stay with Figure 8 before we move on to a different experiment.

MR. SPIEGLER: Okay. Sure. So the -- so in the application the inventors have described that example and the results of that example showing almost no increase. And, you know, I think --

JUDGE ADAMS: Well, I think Judge Fredman presented a very good position. Can you explain why that's not the correct interpretation?

MR. SPIEGLER: Well, I think -- I guess my concern with that, first, is that, you know, I think that we do have a control here that is not

really related to -- you would have expected there would have been some increase of expression, some increase in proliferation with this particular control. You know?

And I think the evidence here is basically, you know -- again, back to the way that the inventors -- they looked at this data and they characterized this as really no increase. And, yes there's -- you know, it's very close to the control, maybe slightly above it. But certainly I don't think one of skill in the art would have viewed this particular result as something that would have given you motivation, especially in view of the inventor's characterization of these results, as something that you would have taken and then applied it to something else.

JUDGE FREDMAN: But in fact, because these things are always multi-genetic, you know, one would also expect that you do need to affect multiple genes in order to induce proliferation. I think very few genes are, alone, capable of doing that.

So the fact that a single gene that's involved doesn't necessarily overwhelm the system isn't necessarily surprising.

MR. SPIEGLER: So I think one answer to that question is, in this case, the actual -- the rejection that's in front of us is the Examiner saying, I'm using these four references to get that element. And in view of what those four references teach I would have then applied it.

And I think here, you know, based on -- like I said, we believe that this evidence, you know, demonstrates that there's really no increase here. This is actual evidence, done at the time of filing, as opposed to what the Examiner has really done, frankly, is -- we believe that the Examiner

essentially read our application, kind of figured out what we were doing, and then kind of worked backwards in an attempt to make --

JUDGE FREDMAN: But -- well, the Examiners typically don't, you know, write -- in advance, so that's still not all that surprising.

MR. SPIEGLER: Yes, absolutely. But the reason why I say that is because, really, if you look at the context of her rejection with respect to these four references, what you have is a very detailed cell-cycle mechanism description. And she's kind of jumping through various hoops to kind of make this connection.

And at the end of the day her conclusion is, you know, these four references give you element C and you would have then combined that with A and B. And here, we've provided evidence that, frankly, the Examiner has never really raised anything about and never really addressed it.

As I said on page 20, we raised it and she said it's not related to the claims. But really it's -- it's actually addressing -- like I said, this is a rare instance where it's not just argument versus argument. We believe we have evidence here against the Examiner's position.

JUDGE ADAMS: You still haven't answered the additive issue. Why do you think this is not an additive effect?

MR. SPIEGLER: Well, I don't -- I think because I'm not sure that we agree with the premise that this -- you know, this is such an increase that, you know -- okay.

Well, let me just address -- even assuming that this showed some slight increase, certainly it's really very close to the control and even if you were to add it to the one that's almost --

JUDGE ADAMS: We can subtract the control out of all three of those lines that are above the control and we're still going to end up with the same effect. I mean, the control is not doing anything at this point. You can't say you have a fivefold effect for one of your lines and say you can't -- that you don't have a twofold effect for the other line because of the control. That just doesn't make sense.

If you're going to subtract the control away from the triangles, you got to subtract the control away from every one of those lines.

MR. SPIEGLER: Right. Okay. Given that, I still think that if you look at the level of proliferation -- the combination of A, B, and C that you show here -- it's actually over fivefold. But agreed, if you subtract out the control, you're really at best -- at best you might think you get some slight additive effect. But certainly not to the level that we see here, I think.

JUDGE ADAMS: Thank you.

MR. SPIEGLER: So really, you know, that -- the basic argument that we've made here kind of applies to the other rationales that we have. Which is basically, you know, we think that there is no reasonable expectation of success. You know, that kind of follows the same argument of why you wouldn't have combined the four references with the primary reference.

JUDGE FREDMAN: Well, the reference is like -- Carrano does say that a small-molecule inhibitor should lead to an increase in cellular

abundance of p27 and the block of proliferation. That's his express statement.

MR. SPIEGLER: So this is in Carrano?

JUDGE FREDMAN: I think so, yes. The final sentence.

MR. SPIEGLER: Carrano -- so in Carrano I believe number one is not related to cardiomyocytes and number --

JUDGE FREDMAN: Cell cycle is in all cells.

MR. SPIEGLER: Cell cycle is in all cells, but you know, again, even assuming that these references are saying to you that -- so is the argument then that -- or the question -- so I understand it, that this is saying that, you know, the SKP2 would inhibit the KIP molecule?

JUDGE FREDMAN: I mean, I think that we have a direct suggestion that this would work.

MR. SPIEGLER: Okay. So let's assume that there's a direct suggestion that this would work. That's a suggestion and we've actually done it. And that's the core of our argument here is that yes, there's a lot of references here that discuss cell cycle regulation, you know, and they make some suggestions, you know, whether it's in cardiomyocytes or fibroblasts, and at the end of the day we actually did it. And we showed here -- the only evidence here is that we did it and it doesn't work or --

JUDGE ADAMS: I mean they have data too though, which shows that it does have an effect.

MR. SPIEGLER: Sorry?

JUDGE ADAMS: Carrano has data that shows it does have an effect.

MR. SPIEGLER: So again --

JUDGE ADAMS: Wait. They have in Figure 6 of Carrano stabilization of cellular p27 by antisense oligo targeting SKP2 mRNA. I mean, so this is not -- and, you know, as you sort of were trying to argue -- evidence against no evidence. I mean, the references themselves do provide evidence -- at least this reference. I think some of the other ones have some data that does disagree with your conclusion.

MR. SPIEGLER: Yeah. One of the things though, about Carrano, that needs to be noted is that, you know, Carrano really -- I mean, the thrust of Carrano, really, if you're reading it in the full context is related also to cancer. And what they say -- for example in the last paragraph -- is that one of the things that you're looking to do is actually to inhibit SKP2, which is actually the opposite of what we're trying to do here.

JUDGE ADAMS: I understand, but it -- so that the -- mechanistically it operates the same way. The question is simply what you're trying to do, your goal. That's simply a -- you know, different people; different goals. It's clear that our primary reference wants to induce proliferation. And yes, I agree. Carrano is not really interested in inducing proliferation ultimately. But what he teaches is what happens.

MR. SPIEGLER: Well, and again -- I mean, part of this, again, and I know that the Examiners are not writing the applications and I mean, part of this is that, again, we've disclosed, you know, our invention and we think the Examiner is kind of -- you know, this is a national -- this application came from Japan. The Japanese typically like to explain their inventions in a lot of detail and that's great for us.

And we think -- kind of -- the Examiner kind of looked at that, said okay -- certainly if you want to walk back and go through the cycle, yes, our invention matches up scientifically. And, you know, you hope that your inventions do.

And really, you know, our position on that is that, you know, yes, certainly you can pick things from certain references and kind of backtrack and find the ultimate invention with respect to, you know, the mechanism. But really, you know, that's kind of a hindsight kind of reconstruction here in this case. And really, what we have is -- at the time there was evidence in hand that C doesn't give you the proliferation, or certainly doesn't give you any real increase and --

JUDGE ADAMS: What does SKP2 do in the cell?

MR. SPIEGLER: So SKP2 is actually -- this actually would be something that falls into element C, which is a factor that inhibits the KIP protein.

JUDGE ADAMS: What does KIP do in the cell?

MR. SPIEGLER: So KIP is a cdk inhibitor and so that -- it's a cdk inhibitor. And the SKP then would essentially inhibit the cdk inhibitor.

JUDGE ADAMS: Okay.

MR. SPIEGLER: And --

JUDGE ADAMS: So if you inhibit the cdk inhibitor you're essentially allowing the cell cycle progression because you have cyclin and cdk present that are doing their thing. Is that right?

MR. SPIEGLER: So if you administer the cdk inhibitor --

JUDGE ADAMS: Right.

MR. SPIEGLER: -- does that mean that you're going to have more cdk?

JUDGE ADAMS: Does it mean that you're going to allow the initiation of the cell cycle because you're releasing the inhibitor of the kinase and you're allowing the kinase and the cyclin to localize to the nucleus and initiate a cell cycle?

MR. SPIEGLER: I don't know that that's -- well, for number one, I don't think that's certainly in any of the references, and number two, you know, I'm not exactly sure to be honest with you.

JUDGE ADAMS: Okay. Okay.

MR. SPIEGLER: Umm --

JUDGE SCHEINER: I'm just checking --

MR. SPIEGLER: Oh, sorry.

JUDGE SCHEINER: You can continue. We're running a little over but --

MR. SPIEGLER: Oh. Oh, sorry.

JUDGE SCHEINER: -- because we asked you a lot of questions.

MR. SPIEGLER: Oh, okay. No. No problem.

JUDGE SCHEINER: That's all right.

MR. SPIEGLER: You know, the only last point I wanted to make is simply just, you know, we have introduced what we believe to be unexpected results here by showing Figure 8 and Figure 10.

And, you know, this is actually kind of important we think. On page 13 of the Examiner's answer we believe that the Examiner

misinterpreted the results that we presented. Ultimately, what we believe she's saying here is we need to almost show that the invention doesn't work or, you know, she wants us to -- because we have the introduction of three genes. It suggests that we need to show that it would not -- the introduction of the three would not result in increased proliferation.

And then she compares that to -- saying, well, what you should have done is compare it to each individual one. But that's not really what -- that's not really what's going on here. Her rejection is taking a reference that teaches A and B and then trying to combine it with something with C.

So in our opinion, we actually made the closest thing you can make to an unexpected -- the best kind of case for unexpected results. We took the closest prior art, A and B -- that gave you a certain level of increase of proliferation. We showed you that C really didn't give you any. So, you know, it's expected to the extent that it would give you the same as the two, or maybe slightly more -- certainly not the effect that we found. And we feel that that's unexpected and we think the Examiner didn't appreciate that argument.

All right. Thank you very much. I appreciate it.

JUDGE SCHEINER: Thank you for coming in.

MR. SPIEGLER: Thanks.

(Whereupon, at 9:26 a.m., the proceedings were concluded.)

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